CASE REPORTS

Median Cerebrofacial Dysgenesis

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THE CONGENITAL CLEFT LIP deformity is usually considered a severe cosmetic defect, and there is general agreement that repair should be undertaken within the first several months of age. Particularly if the deformity is not bilateral (or "double") the prognosis is generally good, and usually there are no other severe deformities associated with the condition. The rare midline cleft lip, however, is often accompanied by severe brain dysgenesis, and it is therefore most important to recognize these cases of arhinencephalia, for the patient is likely not to survive infancy.

To those familiar with the syndrome, children with midline cleft lip and palate present an easily recognized and characteristic appearance. Although cases of this kind are sporadic in occurrence, they are of sufficient frequency to justify an awareness of their quite typical clinical course. Complex interrelationships between the patient and his family demand of the attending physician a knowledge of the patient's capacity for development, the likelihood of recurrence in the family, and a reasoned approach to therapy. The following case underscores these considerations.

Report of a Case

The patient, a 2.08 kg boy, was born to a 30-year-old gravida 8 para 8 woman at 37 weeks of gestation. Arhinencephaly was diagnosed at birth.

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Review of the pregnancy showed no complications. Family history included diabetes mellitus. Two of the patient's siblings had died of nausea, vomiting and dehydration, one at 8 months and the other at 18 months of age.

At birth the patient showed a wide midline complete cleft of the lip, alveolar ridge and palate, and absence of the prolabium, columella, premaxilla and nasal septum. There were no evident extracranial anomalies except undescended testes and a small penis. X-ray films of the skull showed midline defects of the sphenoid and maxillary bones, hypotelorism and absence of nasal bones.

Within the first month of life, the patient was noted to have apneic spells, for which phenobarbital was given. He was discharged at 29 days weighing 5 pounds 13 ounces. He did poorly at home and at age 7 months was put into hospital for pneumonia. He had only gained 1 pound 3 ounces in the first 6 months of life, although the mother obviously loved the child very much and was taking excellent care of him.

Because of the attention focused on this child by the family and their dissatisfaction with gavage feedings, he was readmitted at 8 months for repair of the cleft lip. At this time he was hydrocephalic and he had a high-pitched cry. Through the anterior fontanel, which was 6 cm wide, intracranial contents were bulging. The head transilluminated brilliantly (Figure 1). The patient lay motionless with no prehensile capability, with occasional weak active movements, and with increased tone in all extremities. Generally hyperactive stretch responses were noted and Babinski's sign was evoked bilaterally. He reacted to noxious stimuli only. Cranial nerve examination revealed unequal and poorly reactive pupils, horizontal and vertical nystagmoid movements at rest, absence of doll's-eye responses, and bilateral deafness. An electroencephalogram showed diffuse excessive background slowing. No spinal fluid abnormality was noted. A ventriculogram showed only a thin mantle of cerebral cortex, a large single ventricle, and non-communicating hydrocephalus. Chromosome studies, done twice, showed a normal karyotype.

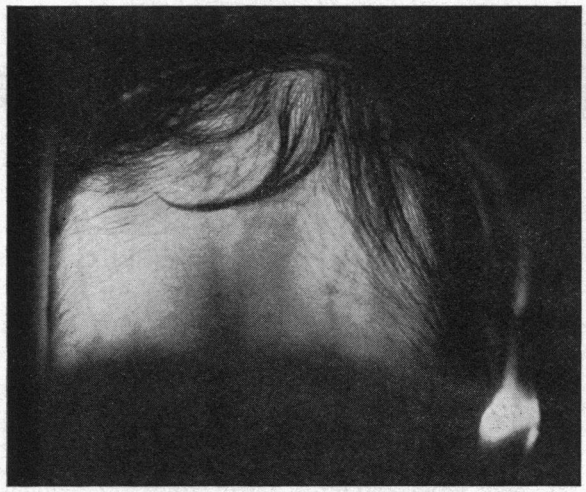

Figure 1.—Photograph showing transillumination of the head.

To enable the parents to feed the child more satisfactorily and to improve his appearance, a straight-line closure of the midline cleft lip was done at 8 months. There were no complications of anesthesia. The patient's temperature was carefully monitored during the procedure, a large silk suture was placed in the tongue and traction was placed on it on several occasions in the postoperative period to relieve obstruction of the upper airway. The wound healed without complication and the patient was discharged on the tenth day. He was able to suck from a premature infant nipple, and improvement in appearance made him more acceptable within the family. Suddenly at age 9 months his pulse rate slowed to 30 per minute and he died shortly thereafter.

At autopsy the brain, which weighed 200 grams, showed massive internal hydrocephalus. The cerebral cortex, 2 to 3 mm thick, was stretched into a thin undivided single ventricle or holosphere, which represented both lateral and third ventricles and communicated with the fourth ventricle by way of the patent cerebral aqueduct. Posteriorly, the ventricular cavity was roofed over by a thin membrane. Olfactory bulbs and tracts and cribriform plate of the ethmoid, corpus callosum, fornix, septum pellucidum, cerebral peduncles and medullary pyramids were conspicuously absent. Cranial nerves II to XII were identified. Anatomical diagnosis included alobar holoprosencephaly in association with a midline facial defect; hypoplasia of thymus, adrenals, testes, and pituitary; bi-lobed right lung with pulmonary congestion; cardiac dilation and acute bronchial pneumonia.

Comment

Although Rudius[1] first observed and recorded a description of similar conditions in 1588, not until 1882 did Kundrat identify the teratologic spectrum which extends by degrees from cyclopia, the most extreme example of midline face and brain anomaly, to the relatively mild absence of the corpus callosum.[2,3,4] Kundrat coined the term *arhinencephaly* because he felt that absence of the olfactory bulb and tract were the cardinal features of this disorder. It has been shown by Yakovlev[5] that the common denominator of these malformations is the failure of evagination of the secondary telencephalic vesicles and of cleavage of the prosencephalon. The supralimbic frontal lobes in front of the gigantopyramidal cortex fail to develop, the olfactory vesicles fail to evaginate and the prosencephalon fails to cleave. Therefore *Holoprosencephaly* has been advanced as a more accurate term than *arhinencephaly* for this malformation, inasmuch as not all rhinencephalic structures are absent.[2]

The typical appearance of median facial anomalies should immediately alert the clinician that dysgenetic intracranial states may coexist. Median cleft lip or bilateral cleft lip with absence of median philtrum and premaxilla and prolabium anlage, associated with orbital hypotelerism, flat nose, microcephaly and sometimes trigonocephaly together, signal the presence of holoprosencephaly with all its attendant implications for impairment of function and threat to life.[3,6] Thus the terms *median cleft lip, cebocephaly, ethmocephaly* and *cyclopia* describe variants of these median facial anomalies which are virtually pathognomic of holoprosencephaly.

It must be emphasized, however, that not all median facial anomalies reflect an underlying brain abnormality. Median cleft nose and median cleft prolabium and premaxilla may occur in combination with cranium bifidum occultum frontalis. Patients with this condition have orbital hypertelorism and, unlike those with midline facial anomalies associated with hypotelorism, are usually not retarded.[7]

When holoprosencephaly occurs with extracephalic abnormalities, the literature suggests the affected patient is likely to have 13-15 (D_1) trisomy.[8,9] This trisomy state, first reported in 1960,

may include cardiac anomalies, abdominal visceral abnormalities, anomalies of the hands, feet and skin, in association with cleft lip and palate, and holoprosencephaly. Although all patients with D_1 trisomy are mentally retarded and all have gross cerebral defects,[8] not all have agenesis of the olfactory bulbs, tracts and trigone.[9] The likelihood of recurrence in the same family of both this trisomy state and normal karyotype holoprosencephaly is not yet known but is probably remote.

In holoprosencephaly apneic spells or seizures, intra- and extra-uterine growth retardation, poikilothermia, spasticity and deficient psychomotor progress are common. These physiological abnormalities together with the structural anomalies such as cleft lip and palate direct the course of therapy. Although patients with alobar holoprosencephaly usually die within the first year, others with less severe variants of this spectrum may have a normal life expectancy.

Diagnosis is based on a careful general examination which includes transillumination of the calvaria (Figure 1). Patients with classical alobar holoprosencephaly have characteristic facies (Figure 2). If orbital hypotelorism and trigonocephaly are demonstrated on skull films, defects of the rhinencephalon and forebrain are probable. Pneumoencephalography shows a large single holosphere which represents common lateral and third ventricles. Chromosome studies occasionally show abnormalities.

Therapeutic efforts beyond the attempt to maintain body temperature and nutrition depend on parental attitudes. Where forces of parental love are compelling, efforts to facilitate feeding and to improve the infant's appearance by repair of the median cleft of lip and palate seem indicated. Surgical repair must be done only with full understanding of the overall prognosis for the infant. These considerations dictated operative intervention in the case here reported.

Summary

A case of alobar holoprosencephaly is described and nosological, embryological, diagnostic and therapeutic implications are reviewed. Surgical correction of facial defects, decried as futile by some physicians, may well facilitate care of infants with this condition in certain circumstances.

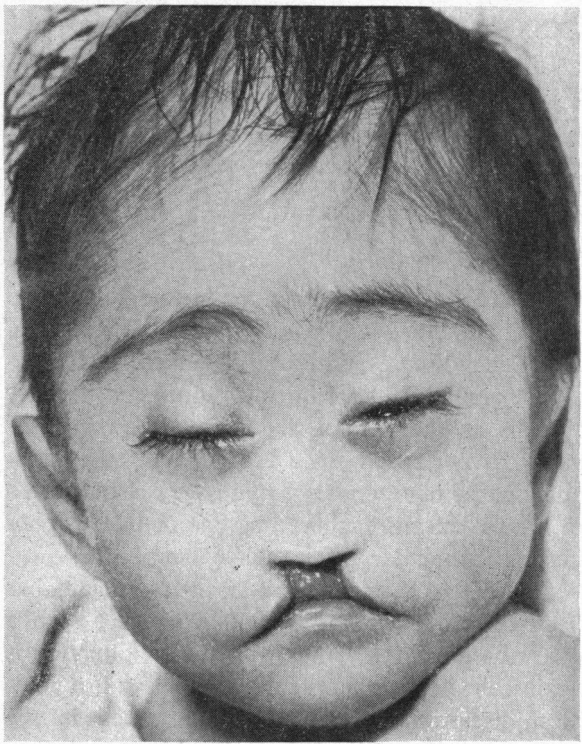

Figure 2. — Typical appearance of patient with alobar holoprosencephaly.

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